

Therapy of Alopecia Areata: On the Cusp and in the Future

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Over the past decade, basic research has established alopecia areata as a T cell-mediated autoimmune disease and has clarified many of its genetic, cellular, and molecular aspects. Perifollicular and intrafollicular mononuclear cell infiltrates directed at anagen hair bulbs are characteristic and striking histologic features in early alopecia areata. The inflammatory infiltrate is composed predominantly of activated CD4 + and CD8 + T cells, together with macrophages and Langerhans cells. The initiation phase of alopecia areata is mediated by type 1 cytokines, including interleukin-2, interferon- γ , and tumor necrosis factor- α . Like other diseases with a strong autoimmune component, alopecia areata has as-

sociated with it specific human leukocyte antigens, which determine susceptibility, severity, chronicity, and resistance. New topical immunomodulating drugs and biologic therapies that have been developed, or that are in development, for the treatment of other immune-mediated inflammatory skin diseases will likely be effective in alopecia areata as well. The present discussion addresses the treatment of alopecia areata within the framework of these new modalities. **Keywords:** lymphocytes/macrophages/Langerhans cells/immunomodulating drugs/biologic therapies. *JID symposium Proceedings* 8:207–211, 2003

Alopecia areata (AA) disrupts many lives, young and old, because of its recurrent episodes of erratic, unpredictable, patchy hair loss and sometimes long-standing loss of all scalp hair (alopecia totalis, AT) or loss of all scalp and body hair (alopecia universalis, AU). Over the past decade, the International Research Workshops on Alopecia Areata have stimulated essential basic research in this disease. These efforts, supported in large part by the National Alopecia Areata Foundation (NAAF), have established AA as a T cell-mediated autoimmune disease (Gilhar *et al*, 1998; Gilhar *et al*, 2001) and have clarified many of its genetic, cellular, and molecular aspects. As a result, new therapies will likely become available to those who suffer from AA.

Approximately 2% of the population are at a lifetime risk of suffering from AA, which occurs worldwide (Safavi *et al*, 1995). Hair loss usually occurs in distinct bare patches on the scalp. In approximately 5% of cases, the disease progresses to AT/AU (Safavi *et al*, 1995). Persons with AA are usually otherwise healthy, and the disease occurs in all age groups, although children and young persons are affected most commonly.

Perifollicular and intrafollicular mononuclear cell infiltrates are characteristic and striking histologic features in early AA. The inflammatory infiltrate is directed at anagen hair bulbs and is composed predominantly of activated CD4 + and CD8 + T cells, together with macrophages and Langerhans cells (Bodemer *et al*, 2000; Gilhar *et al*, 2002). The intrafollicular infiltrate is composed predominantly of CD8 + T cells, in contrast to the perifollicular infiltrate, which is composed primarily of CD4 + T cells (Todes-Taylor *et al*, 1984; Khoury *et al*, 1992; Gilhar *et al*, 2002). Depletion

of either activated CD8 + or CD4 + T cells restores hair growth in the Dundee experimental bald rat (DEBR) model (McElwee *et al*, 1996; McElwee *et al*, 1999). A T cell-directed therapeutic approach may also be relevant for hair regrowth in humans. The fact that there is no obvious cellular destruction or any progressive cumulative damage in AA suggests that the presence of CD8 + T cells may signal not a cytotoxic role in AA but rather a regulatory or suppressor cell function. Scalp biopsies from patients and from the AA mouse model show a heavy presence of type 1 cytokines, including interleukin-2 (IL-2), interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α) (Hoffmann *et al*, 1994; Hoffman, 1999; Carroll *et al*, 2002). Possible therapies may include agents directed against these cytokines.

As with other diseases with a strong autoimmune component, specific human leukocyte antigens (HLA) are associated with AA and determine susceptibility, severity, chronicity, and resistance (Welsh *et al*, 1994; Price and Colombe, 1996; Colombe *et al*, 1999). The HLA class II allele, DQB1*03, is a general marker for AA susceptibility and is present in over 80% of all AA patients. Moreover, the allele DRB1*1104 is over 10 times more frequent in all types of AA than in a control population. Markers for severity and chronicity appear to be HLA-DQB1*0301 and DRB1*0401, which are both significantly increased in long-standing AT and AU. Two clinical types of AA, patchy AA and AT/AU, are thus distinguishable at the molecular level by a genetically based predisposition to the extent of disease.

Current traditional therapies are predominantly immunomodulating modalities, including corticosteroids, topical immunotherapy, anthralin, and photochemotherapy (PUVA). A nonspecific modality is topical minoxidil, which prolongs anagen and promotes growth of longer and wider hair (Price, 1999; Wiseman *et al*, 2001). These treatments have been used for many years, and new targeted therapies are particularly needed for children, for those with chronic, persistent patchy disease, and for those with AT and AU (the most extensive forms of the disease).

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Abbreviations: AA, alopecia areata; HLA, human leukocyte antigens.

THERAPIES FOR ALOPECIA AREATA: "ON THE CUSP"

New topical immunomodulating drugs and biologic therapies have been developed, or are in development, for the treatment of immune-mediated inflammatory skin diseases such as atopic dermatitis and psoriasis (Krueger, 2002; Singri *et al*, 2002). This has followed years of basic research, which has helped to clarify the complex immunopathogenesis for both of these diseases. Over the past decade, extensive basic research has shown that AA is also a T cell-mediated autoimmune skin disease, with many features similar to psoriasis, and that it is an excellent candidate for these same therapies.

The immunopathologic features of psoriasis have provided the basis of a conceptual model for rationally designed biologic therapies. Gordon and colleagues have suggested four strategies within this model: (i) reduction of pathogenic T cells, (ii) inhibition of T cell activation, (iii) shifting a type 1 cytokine response to a type 2 response, and (iv) blocking activity of inflammatory cytokines (Singri *et al*, 2002). This therapeutic model is also applicable to the new immunomodulating drugs used in atopic dermatitis. The present discussion addresses the treatment of alopecia areata in the framework of this conceptual model.

New Immunomodulatory Therapies Topical immunomodulators are a new class of agent that acts locally on T cells by suppressing cytokine transcription (Schneider, 2002). The two most studied topical immunomodulators are tacrolimus and pimecrolimus. A third new member of this group is topical cyclosporine (CsA). All three drugs inhibit calcineurin, thereby inhibiting IL-2 production.

Topical tacrolimus (Protopic) Tacrolimus has been used for many years to prevent organ rejection after liver or kidney transplantation. It acts directly on T cells to inhibit IL-2 transcription, which results in decreased growth and proliferation of T lymphocytes in response to foreign antigens (Lawrence, 1998). It also inhibits other cytokines, including TNF- α and IFN- γ , both important in T cell activation. Like other systemic immunosuppressants, *oral* tacrolimus is associated with significant side effects, such as kidney and liver impairment and hypertension. Several studies have demonstrated the safety and efficacy of *topical* tacrolimus ointment in patients with atopic dermatitis. The topical formulation has been studied in more than 10,000 patients worldwide and appears to have no significant systemic side effects (Schneider, 2002). It is FDA-approved for treatment of atopic dermatitis in children two years of age or older and on all parts of the body, including the face. Tacrolimus ointment does not cause skin atrophy, pigment changes, or telangiectasia.

The ointment formulation, however, may not be optimal for AA (Thiers, 2000). A clinical trial in patients with AA was recently completed in the Department of Dermatology, University of California, San Francisco. Seventeen patients, with AA, affecting 25% to 75% of the scalp for more than 12 months, were enrolled in a single-center, open-label study. Tacrolimus ointment 0.1% was applied twice daily for 24 weeks, and patients were observed for six additional weeks after stopping treatment. Six patients dropped out of the study because the ointment formulation was too greasy for the scalp or because of scheduling problems. Eleven patients completed the study, and all showed either no change in their hair growth or further hair loss (Submitted for publication). Another study reported five patients with long-standing, treatment-resistant alopecia universalis who applied 0.1% tacrolimus ointment once daily for six months; none had hair regrowth (Feldmann *et al*, 2002). Treatment failure in patients with long-standing alopecia universalis is not surprising, as their response to existing treatments is generally poor and they may not be appropriate for evaluating the efficacy of new modalities.

Perhaps hair growth promotion with immunomodulatory agents such as tacrolimus will be more successful in patients who still have a dense dermal T cell infiltrate, as in patients whose AA is of short duration (i.e., 3–12 months) or who have chronic, active patchy disease. In such patients, larger, placebo-controlled trials are necessary for assessing results. A less greasy formulation of tacrolimus may improve drug delivery, efficacy, and compliance with scalp application.

Topical pimecrolimus (Elidel) Pimecrolimus, an ascomycin derivative, is a cell-selective cytokine inhibitor developed for the treatment of inflammatory skin diseases (Meingassner *et al*, 1997). It binds to macrophilin-12; inhibits calcineurin; inhibits synthesis of inflammatory cytokines, such as IL-2 and IFN- γ ; and inhibits T cell and mast cell activation. Pimecrolimus has high skin-specific anti-inflammatory activity with low potential for affecting the systemic immune response. The cream 1% formulation is safe and effective for atopic dermatitis and does not cause skin atrophy or telangiectasia (Eichenfield *et al*, 2002). Unfortunately, the cream is not expected to be effective for hair regrowth because it permeates no lower than the superficial dermis, which is an insufficient depth for targeting T cells involved in AA. *Oral* pimecrolimus is in clinical trials in psoriasis and, like the cream formulation, does not cause systemic immunosuppression and is inactive in transplant models. Clinical trials with the oral drug are eagerly awaited in AA.

Topical cyclosporine A (PsorBan) The use of oral CsA to treat severe inflammatory skin diseases is well established. Oral CsA is also effective in the short-term treatment of alopecia areata (Gupta *et al*, 1990); however, the inherent toxicity associated with systemic administration precludes its value in treating chronic skin diseases that, while serious, are not life threatening. In the past, topical formulations of CsA were ineffective because of poor skin penetration. To surmount this problem, a heptamer of arginine was conjugated to CsA through a pH-sensitive linker designed to release CsA at physiologic pH within the skin (Rothbard *et al*, 2000). The oligoarginine transporters enable full-skin-thickness penetration of CsA into cells throughout the epidermis and dermis of murine and human skin, with functional inhibition of cutaneous inflammation.¹

Preclinical safety testing with topical CsA has been completed, and the formulation has a clean toxicity profile. A phase II multicenter psoriasis study is in progress. Clinical trials in AA with topical CsA are pending and will be of great interest, although the current formulation is greasy and designed for glabrous skin and so reformulation for the scalp will be needed.

New Biologic Therapies Biologic agents are proteins that possess pharmacologic activity and can be extracted from tissue. With the development of recombinant DNA technology, biologic agents can be synthesized in large quantities and designed to alter specific physiologic responses (Singri *et al*, 2002). Biologic therapies target cell surface receptors, and their theoretical advantage is that their greater specificity will provide better safety profiles. Biologics are larger than "small-molecule" drugs and are most often administered by injection (subcutaneous, intramuscular, or intravenous).

AA is mediated by activated T cells. The process of activation requires two signals between T cells and antigen-presenting cells (APCs). Signal 1 involves the presentation of a specific antigen by the MHC (HLA) molecule on the surface of the APC and its recognition by its specific T cell receptor on the surface of the T

¹Lin Q, Rothbard JB, Garlington S, McGrane P, Wender P, Khavari PA: Addition of a poly arginine linker to cyclosporin A facilitates transcutaneous delivery and topical inhibition of cutaneous inflammation. *J Invest Dermatol* 114:777, 2000 (abstr)

cell (**Fig 1**). At present, the specific antigen(s) involved in AA is not known, although a melanocyte-related protein has been suggested in some patients (Gilhar *et al*, 2001). After T cell recognition of the antigen, a second costimulatory signal must be delivered by the APC to lead to full T cell activation. Costimulation involves several interactions (some of which are shown in **Fig 1**); these molecules are the targets of many biologic drugs now used to block T cell activation.

Four biologic agents are briefly described below. They include etanercept, infliximab, efalizumab, and alefacept. These agents have been developed for rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and psoriasis. None has been tested in AA, but, because medications that are successful in treating psoriasis have been effective in treating AA, clinical trials in AA are warranted. The nomenclature of the biologic therapies is regulated so that the suffix of the name denotes the therapy's class: *-ximab* denotes a chimeric monoclonal antibody, as in *infliximab*; *-zumab* denotes a humanized monoclonal antibody, as in *efalizumab*; and *-cept* denotes a receptor-antibody fusion protein, as in *etanercept* and *alefacept*.

Etanercept (Enbrel) Etanercept is a human fusion protein that inhibits the inflammatory cytokine TNF- α . It is FDA approved for the treatment of rheumatoid arthritis (since November 1998), juvenile rheumatoid arthritis (since May 1999), and psoriatic arthritis (since January 2002) and is given twice weekly as a subcutaneous injection. Clinical trials with etanercept in psoriasis have been promising (Mease *et al*, 2000; Gottlieb and Weinstein, 2003). At present, the agent is considered to have a good margin of safety in psoriasis, although safety related to its long-term use needs to be determined.

Infliximab (Remicade) Infliximab inhibits the inflammatory cytokine TNF- α and is a chimeric (mouse/human) antibody. It is FDA approved for the treatment of rheumatoid arthritis and Crohn's disease. Controlled clinical trials in psoriasis show promise of infliximab's rapid efficacy (Chaudhari *et al*, 2001). It is administered by intravenous infusion over 90 minutes.

The long-term safety of TNF- α inhibition is being monitored in North America and Europe. Rare instances of tuberculosis activation, multiple sclerosis, positive antinuclear antibodies, lymphoma, and pancytopenia have been reported (Gottlieb, 2003). Most patients with such side effects were on concomitant

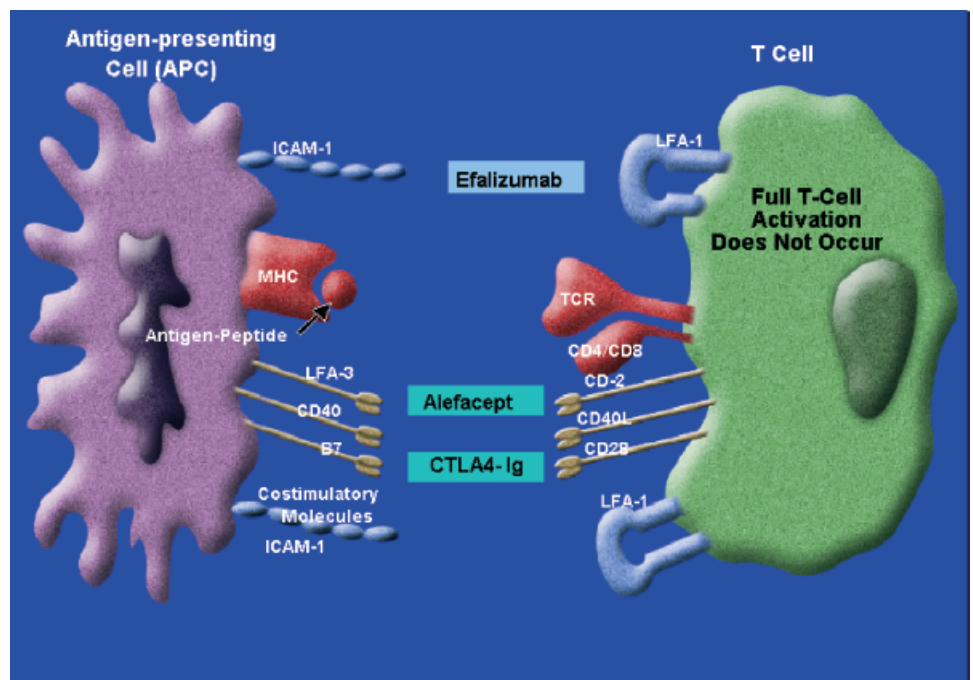
immunosuppressive therapy for rheumatoid arthritis or Crohn's disease, and no causal relationship has been established between these events and the use of TNF- α inhibitors.

Efalizumab (Raptiva) Efalizumab is a humanized monoclonal antibody that has several effects of potential therapeutic benefit in AA. It binds CD11a, a component of LFA-1 that binds to ICAM-1 on APCs, and thus it interrupts this costimulatory signal (**Fig 1**). It also blocks T cell adhesion to endothelial cells and T cell migration (trafficking) into inflamed tissues. In phase II clinical trials, 62% of patients showed 50% improvement as measured by the Psoriasis Activity and Severity Index (PASI), and 30% showed 75% improvement. Other than mild flu-like symptoms that subsided with continued use of the medication, there were no significant infections in these clinical studies (Papp *et al*, 2001; Gottlieb *et al*, in press). The drug is given by subcutaneous injection once weekly by the patient. Application for approval in the United States has been submitted.

Alefacept (Amevive) Alefacept is a fusion protein that induces apoptosis in T cells expressing high levels of CD2. It also may block the LFA-3/CD2 costimulatory signal (**Fig 1**). Alefacept reduces high CD2-expressing memory T cells in the circulation. It is FDA approved (since February 2003) for the treatment of psoriasis. Monitoring of the CD4 + T cell count is required with alefacept. In phase II trials in psoriasis, this agent has shown efficacy with an excellent safety profile. In one psoriasis trial (Krueger *et al*, 2002), 71% of patients showed 50% or greater improvement in PASI, 40% had 75% or greater improvement, and there was no increased incidence of infection. Some patients had a remission for eight months, which may reflect slow repopulation of the skin with native T cells (Singri *et al*, 2002). The medication is given once weekly either intramuscularly or by an intravenous bolus ("push").

Biologics in Development In addition to the agents described, many other biologics are in development. For example, CTLA4Ig is a fusion protein that blocks CD80/86 (B7) costimulation with CD28 (**Fig 1**) and is administered by intravenous infusion. Clinical trials have been conducted in psoriasis (Abrams *et al*, 1999) and are in progress in rheumatoid arthritis. As a word of caution, long-term incidence of auto-

Figure 1. Antigen-presenting cell (APC)-T cell interactions needed for T cell activation. The MHC complex presents a specific antigen to the T cell receptor, referred to as signal 1. Multiple interactions are needed for costimulation, referred to as signal 2. Sites of blockade of T cell activation by three biologic agents are shown. ICAM-1 indicates intracellular adhesion molecule-1; LFA, lymphocyte function-associated antigen; MHC, major histocompatibility complex; and TCR, T cell receptor.



immune disease, infection, and cancer has yet to be determined for the biologic therapies.

IN THE FUTURE

The following concepts may not reach therapeutic fruition for AA as soon as those described above. Conceptually, however, they target specific physiologic responses found in human or animal AA and are based on the four strategies proposed by Gordon and colleagues for rationally designed biologic therapies in psoriasis (Singri *et al*, 2002). Treatments that are effective in psoriasis have been used in AA, and some approaches are showing promise in psoriasis clinical studies (Kirby and Griffiths, 2002). They are mentioned for this reason.

Reduction of pathogenic T cells Both CD4+ and CD8+ T cells are required and closely interact to maintain an AA lesion on the human scalp (Gilhar *et al*, 2002). Not surprisingly, depletion of either or both promotes hair regrowth in the AA rat model (McElwee *et al*, 1996; McElwee *et al*, 1999). In psoriasis, alefacept binds specifically to T cells expressing high levels of CD2 and, when given in therapeutic doses, reduces circulating memory T cells. Other agents to reduce the number of pathogenic T cells are in development.

Inhibition of T cell activation/migration Blockade of T cell activation with CTLA4Ig has delayed AA onset in the mouse model by blocking the costimulatory interaction of CD28-B7 (Carroll *et al*, 2002). CTLA4Ig is in clinical trials for rheumatoid arthritis, and trials in AA would be appropriate.

Blockade of T cell migration using an anti-CD44v10 monoclonal antibody prevents the onset of AA in the C3H/HeJ mouse graft-induced model (Freyschmidt *et al*, 2001). CD44v10 is a lymphocyte cell surface receptor found on T cells in lesional AA skin; hence, the use of anti-CD44v10 antibodies might be a future therapeutic approach to inhibit the development of AA.

Shifting a type 1 cytokine response to a type 2 cytokine response The manipulation of the type 1/type 2 cytokine balance by exogenously administered cytokines is a therapeutic strategy termed *immune deviation*. Untreated AA is characterized by a type 1 cytokine response, and successful treatment with a contact sensitizer such as diphenylprone is associated with increased expression of interleukin-10 (IL-10), a type 2 cytokine. Another aspect of AA is that there is no destruction of hair follicles in AA, and this has been attributed in part to a shift from a type 1 cytokine response to a more chronic type 2 cytokine immune profile. For these reasons, administration of IL-10 is a possible therapeutic approach for AA. In fact, recombinant human IL-10 was given subcutaneously in a recent phase II trial in 10 patients with psoriasis, with antipsoriatic effect confirmed by histological examination (Asadullah *et al*, 1999). Initial positive results have, however, been tempered by more negative results in a double-blind, placebo-controlled study (Kimball *et al*, 2002). Recently, IL-4 therapy, which also induces a type 2 cytokine differentiation, was given to patients with severe psoriasis and produced significant clinical improvement (Ghoreschi *et al*, 2003). This approach may thus have potential as a treatment for type 1-associated autoimmune diseases such as psoriasis and AA.

Blocking activity of inflammatory cytokines Another strategy is the selective targeting of specific inflammatory cytokines. Two TNF- α inhibitors were described above. Expression of the inflammatory cytokine IFN- γ is increased in psoriatic lesions. A humanized monoclonal antibody against human IFN- γ (HuZAF) is in clinical trials in psoriasis and other type 1 cytokine-mediated diseases. If successful, this approach would be desirable because global immune suppression is not produced by blocking this cytokine (Krueger, 2002).

SUMMARY

AA has been established as a T cell-mediated autoimmune disease with a type 1 cytokine pattern. New immunomodulators and biologic therapies target specific immunologic responses and offer new strategies for treating pathogenic T cells and the cytokines they produce. In the future, AA should receive first-line consideration for clinical studies with new specific therapies for T cell-mediated inflammatory diseases.

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